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EXAMINER	
CANELLA, KAREN A	

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1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,432	PLOWMAN ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,17-22 and 26-33* is/are rejected.

7)☐ Claim(s) *14-16 and 23-25* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/3/08, 8/2/06, 8/8/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-33 are pending and examined on the merits.

It is noted that MAP2K6 is synonymous with MEK6, MKK6, PRKMK6, mitogen activated protein kinase kinase-6.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 3, 5, 28 and 31-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "small" in claims 2 and 28 is a relative term which renders the claim indefinite. The term "small" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Section 2173 of the M.P.E.P. states

Claims Must Particularly Point Out and Distinctly Claim the Invention

The primary purpose of this requirement of definiteness of claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent..

In the instant case, the specification does not provide a limiting definition for a "small" molecule modulator which would provide a boundary between that which is "small" versus that which is not small, or "medium". Thus, a potential infringer would not be able to ascertain when a molecule was large enough not to be considered small, and therefore outside the scope of the claims.

Claim 31 is vague and indefinite in the recitation of "MBM" which ha no literal support in the specification. For purpose of examination, "MBM" will be read as modifier of branching morphogenesis.

Claim 33 is vague and indefinite because of reliance on Table I in the specification. Section 2173.05(s) of the M.P.E.P. states

Where possible, claims are to be complete in themselves. Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. Incorporation by reference is a necessity doctrine, not for applicant's convenience." Ex parte Fressola, 27 USPQ2d 1608, 1609 (Bd. Pat. App. & Inter. 1993)

Claim 33 is vague and indefinite in the recitation of "having a >25% expression level" without stating to what the expression level is being compared to.

Claims 5 and 28 are vague and indefinite n the recitation of "nucleic acid modulator". It is unclear if "nucleic acid" defines the nature of modulator itself, or if "nucleic acid" is intended to define the target of the modulation. For purpose of examination, both alternatives will be considered.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re wands, 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir. 1988)..

Claim 17 requires in part "an agent derived therefrom" with respect to the test agent of claim 1. The specification provides no guidance as to how an agent is actually derived from the test agent of claim 1, nor does it teach the structural alterations which should be enacted upon the test agent of claim 1 in order to produce the test agent derived therefrom. given the lack of guidance in the specification regarding the structural characteristics of a test agent derived therefrom, one of skill in the art would be subjected to undue experimentation without reasonable expectation of success in order to make said test agent(s) in order to carry out the method of claims 17-25.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 5, 31-33 rejected under 35 U.S.C. 102(b) as being anticipated by Wong et al (Gynecologic Oncology, August 2001, Vol. 82, pp. 305-311).

Claim 1 is drawn to a method comprising (a)providing an assay system comprising a MAP2K6 polypeptide or nucleic acid, (b) contacting the assay system with a test agent under conditions whereby, but for the presence of the test agent, the system provides a reference activity and (c)detecting a test agent-biased activity of the assay system. Claim 5 embodies the

method of claim 1, wherein the assay system comprises an expression assay and the candidate test agent is a nucleic acid modulator.

Claim 31 is drawn to a method for diagnosing a disease in a patient comprising (a)obtaining a biological sample from a patient, (b) contacting the sample with a probe for a modulator of branching morphogenesis. Claim 32 embodies the method of claim 31 wherein said disease is cancer. Claim 33 embodies the method of claim 32 wherein said cancer is shown in Table I as having greater than 25% expression level.

Wong et al disclose a method comprising measuring the expression level of MAP2K6 polynucleotides normal, preneoplastic and neoplastic ovarian cell lines and ovarian surface epithelial cells obtained from patients(page 306, under the heading of "Cells and Cell Lines" in the presence and absence of hepatocyte growth factor (HGF) (Figure 1). Ovarian cancer is listed in the instant Table I as having a 26% expression level thus fulfilling the limitations of claim 33.

It is noted that the recitation of a method "of identifying a candidate branching morphogenesis modulating agent" and a "method for diagnosing a disease in a patient" has not been given patentable weight because said recitations occur in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See In re Hirao, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

It is further noted that the phrase "wherein a difference between the test agent-biased activity and the reference activity identifies the test agent as a candidate branching morphogenesis modulating agent" are not given patentable weight when comparing the claims to the prior art as it simply expresses the intended result of a process step positively recited, see MPEP 2111.04.

Further, steps (c) and (d) are not given patentable weight as they are confined to mental steps, rather than to active method steps

Given that the method of the prior art comprises the same method steps as claimed in the instant invention, the claimed method is anticipated because the method will inherently be a method for

identifying a candidate branching morphogenesis modulating agent and a method for diagnosing a disease in a patient. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

Claims 1-6, 17, 19, 26-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Stein et al (WO 97/22704).

Claim 2 embodies the method of claim 1 wherein the assay system comprises a MAP2K polypeptide and the candidate test agent is a small molecule modulator. Claim 3 embodies the method of claim 2 wherein the screening assay is a kinase assay. Claim 4 embodies the method of claim 1, comprising a MAP2K polypeptide and an antibody as the candidate test agent. Claim 6 embodies the method of claim 5 wherein the nucleic acid modulator is an antisense oligomer.

Claim 17 is drawn to the method of clam 1 further com[rising (d) providing a second assay system comprising cultured cells, (e)contacting the second assay system with the test agent of (b) under conditions whereby but for the presence of the test agent, the system provides a reference activity; and (f)detecting an agent-biased activity of the second assay system, wherein the second assay system includes a second assay that detects and agent-biased change in an activity associated with branching morphogenesis. Claim 19 embodies the method of claim 17 wherein the second assay system comprises cultures cells.

Claim 26 is drawn to a method comprising contacting a mammalian cell with an agent that specifically binds a MAP2K6 polypeptide or nucleic acid. Claim 27 embodies the method of claim 26 wherein the agent is administered to a mammalian animal predetermined to have a pathology associated with branching morphogenesis. Claim 28 embodies the method of claim 26 wherein the agent is a small molecule modulator, a nucleic acid modulator or a antibody. Claim 29 embodies the method of claim 26 wherein the branching morphogenesis is angiogenesis. Claim 30 embodies the method of claim 29 wherein tumor cell proliferation is inhibited.

It is noted that the phrase of claim 29, "wherein the branching morphogenesis is angiogenesis" and the phrase of claim 30 "wherein tumor cell proliferation is inhibited" are not given patentable weight when comparing the claims to the prior art as the phrases simply expresses the intended result of a process step positively recited, see MPEP 2111.04.

Stein et al disclose a method for identifying a composition which affects MEK6 activity comprising incubating said composition and MEK6 kinase or a polynucleotide encoding said kinase for a time sufficient to allow the components to interact ad measuring the effect of the composition of MEK6 kinase or the polynucleotide encoding the kinase, under conditions whereby but for the presence of the test agent, the system provides a reference activity and (c) detecting a test-agent biased activity of the assay system (claim 24, figures 4, 5 and 7a, column 12, lines 16-18). Stein et al disclose that test agent may include antibodies which neutralize MEK6, a competing peptide that represents the substrate binding domain of MEK6 or the dual phosphorylation motif of the MEK6 substrate, an antisense polynucleotide or ribozyme that interferes with the transcription or translation of MEK6, or a molecule that prevents transfer of phosphate groups from MEK6 to a substrate (page 7, lines 29-35). Stein et al disclose that ansiomycin treatment or exposure to UV light was able to activate MEK6 (page 24, lines 6-11) which fulfills the specific embodiment of "modulate". Stein et al disclose a second assay system comprising a coupled in vitro kinase assay to measure the activity of p38 in response to MEK6 (page 11, line 18 to page 12, line 36) which fulfills the specific embodiment of claim 17 with respect to the second assay system. Stein et al disclose that antibodies and other agent having a desired effect on MEK6 activity may be administered to a patient to treat an existing disease in vivo, and that an agent which decreases MEK6 activity in vivo may be administered to treat inflammation, autoimmune diseases, cancer or degenerative diseases (page 17, lines 27-31) which fulfills the specific embodiment of claims 29-30.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6 and 17, 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stein et al (WO 97/22704).

Claim 20 embodies the method of claim 17 wherein the second assay detects an event selected from a group including cell proliferation and cell cycling.

Stein et al teach that diseases associated with the p38 cascade include any disorder linked to MEK6 kinase activity including cell-growth related diseases such as cancer, metabolic diseases, abnormal cell growth and proliferation, or cell cycle abnormalities (page 13, lines 11-20). Stein et al teach the MEK6 assay coupled with the p38 kinase assay (above). Stein et al do not specifically teach an assay which would measure cell proliferation and cell cycling.

It would have been prima facie obvious at the time the claimed invention was made to do an assay which would measure alterations in cell proliferation or cell cycling in conjunction with the second p38 assay. One of skill in the art would have been motivated to do so by the teachings of Stein et al on the diseases associated with the p38 cascade. One of skill in the art would understand based on the teachings of Stein et al that modulation of cell proliferation and modulation of cell cycling can result from modulation of p38 activity as a result of modulation of MEK6 activity.

Claims 1-6, 8-11 and 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stein et al (WO 97/22704)in view of Sodhi et al (Cancer Research, 2000, Vol. 60, pp. 4873-4880).

Claim 8 embodies the method of claim 1 wherein the assay system comprises cultured cells expressing MAP2K6 and wherein the system includes an assay that detects an agent-biased change in branching morphogenesis. Claim 9 specifies that said branching morphogenesis is

angiogenesis. Claim 10 specifies that the assay system comprises cultured cells. Claim 11 embodies the method of claim 11 wherein the assay detects a response to hypoxic conditions. Claim 18 embodies the method of claim 17 wherein the second assay system detects an agent-biased change in an activity associated with angiogenesis. Claim 20 embodies the method of claim 19 wherein the second assay detects a response to hypoxic conditions.

Stein et al renders obvious the detection of modulation in cell proliferation and cell cycling as a result of modulation of p38 resulting from modulation of MEK6 for the reasons set forth above. Stein et al do not teach or suggest the detection of an event which is a response to hypoxic conditions or angiogenesis.

Sodhi et al teach that both the MAPK pathway and the p38 pathway acts by modulating the phosphorylation state of HIF-1 in response to hypoxic conditions which results in the upregulation of VEGF and subsequent angiogenesis (page 4879, Figure 6). Sodhi et al teach that these finding provide the first insight into a mechanism whereby inflammatory cytokines and cellular stresses which activate p38 can interact with the hypoxia-dependent machinery of angiogenesis (abstract, last eight lines).

It would have been prima facie obvious at the time the claimed invention was made to measure the relative response of MEK6 and p38 to hypoxic stimuli by measuring angiogenesis. One of skill in the art would have been motivated to do so by the teachings of Sodhi et al which link the activation of MEK6 ((MKK6) and p38 to the activation of Hif-1alpha and subsequent angiogenesis.

Claims 1-6, 8, 9, 11,17, 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stein et al (WO 97/22704) in view of Terada et al (Kidney International, 1999, Vol. 56, pp. 1258-1261).

Stein et al renders obvious the detection of modulation in cell proliferation and cell cycling as a result of modulation of p38 resulting from modulation of MEK6 for the reasons set forth above. Stein et al teach diseases associated with the p38 cascade include any disorder linked to MEK6 kinase activity including cell-growth related diseases such as cancer, metabolic diseases, abnormal cell growth and proliferation, or cell cycle abnormalities (page 13, lines 11-

20). Stein et al teach the MEK6 assay coupled with the p38 kinase assay (above). Stein et al do not specifically teach an assay which would cell cycling.

Terada et al teach that TGF-beta activates the TAK1-MKK6-p38 pathway and results in a transcriptional down-regulation of cyclin D1 (pages 1259-1260, under the heading of "Down-regulation of cyclin D1 Expression by the TAK1-MKK6-p38 Pathway").

It would have been prima facie obvious at the time the invention was made to measure cell cycling and cyclin D1 expression in the method of Stein et al. One of skill in the art would have been motivated to do so by the teachings of Terada et al on the negative regulation of cyclin D1 by the MKK6-p38 pathway.

Claims 1-6, 8-13, 17-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stein et al (WO 97/22704) in view of Matsumoto et al (Journal of Cell Biology, January 2002, Vol. 156, pp. 149-160).

Claim 11 embodies the method of claim 10 wherein the assay detects tubulogenesis. Claim 12 embodies the method of claim 10 wherein the assay detects tubulogenesis, and wherein the assay system comprises the step of testing the cellular response to stimulation with at least two different pro-angiogenic agents. Claim 13 embodies the method of claim 10 wherein the assay detects tubulogenesis and wherein the cells are stimulated with an inflammatory angiogenic agent. Claim 20 embodies the method of claim 19 wherein the second assay detects tubulogenesis. Claim 21 embodies the method of claim 20, wherein the assay detects tubulogenesis, and wherein the assay system comprises the step of testing the cellular response to stimulation with at least two different pro-angiogenic agents.. Claim 22 embodies the method of claim 20, wherein the assay detects tubulogenesis and wherein the cells are stimulated with an inflammatory angiogenic agent.

Stein et al teach that diseases associated with the p38 cascade include any disorder linked to MEK6 kinase activity including cell-growth related diseases such as cancer, metabolic diseases, abnormal cell growth and proliferation, or cell cycle abnormalities (page 13, lines 11-20). Stein et al teach the MEK6 assay coupled with the p38 kinase assay (above). Stein et al do not specifically teach an assay which would measure tubulogenesis and/or apoptosis along with the cellular response to at least two different pro-angiogenic agents.

Matsumoto et al teach that activation of p38 is induced by FGF-2 in endothelial cells undergoing tubular morphogenesis in culture, but that treatment with p38 inhibitors and dominant negative upstream regulators of p38 (such as dominant negative MKK6, page 152, first column, line 18 to second column, line 4) enhanced FGF-2 mediated tubular morphogenesis by regulating differentiation, apoptosis and proliferation of the endothelial cells (page 156, first paragraph under "Discussion"). Matsumoto et al teach that VEGF, which is proangiogenic in the chick chorioallantoic membrane did not activate p38 in vascular endothelial cells.

It would have been prima facie obvious at the time the claimed invention was made to extend the MEK6 and p38 coupled expression assays of Stein et al to measurement of tubulogenesis and apoptosis in the response of the assay system to the pro-angiogenic agents of FGF-2 and VEGF. One of skill in the art would have been motivated to do so by the teachings of Matsumoto et al linking the activation of p38 to the negative regulation of the tubulogenic response to FGF-2 and the induction of VEGF-mediated tubulogenesis without activation of p38. One of skill in the art would be motivated to determine if MKK6 was activated or not by FGF-2, and one of skill in the art would also be motivated to determine if a different kinase from MEKK6 controlled FGF-2 activation of p38. One of skill in the art would be motivated to include VEGF as a positive control for non-p38 modulated tubulogenesis.

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stein et al (WO 97/22704). Claim 7 embodies the method of claim 6, wherein the nucleic acid modulator is a "PMO" (phosphorodiamidate morpholino oligomer).

Stein et al teach that test agent may include an antisense polynucleotide or ribozyme that interferes with the transcription or translation of MEK6 (page 7, lines 29-35). Stein et al do not specifically teach that the antisense polynucleotide is a phosphorodiamidate morpholino oligomer.

Iversen teaches that sterically hindered oligonucleotides, such as are not associated with activation of RNase and are therefore termed "RNase resistant" which reduces unwanted side effects relative to a non-modified "natural oligonucleotide" the inappropriate cleavage of non-target RNA heteroduplexes and binding to cellular proteins (page 7, lines 1-13).

It would have been prima facie obvious at the time that the claimed invention was made to use a phosphorodiamidate morpholino oligomer rather than a natural oligomer as the antisense agent taught by Stein et al. One of skill in the art would have been motivated to do so by the teachings of Iversen on the improvement afforded by using RNase resistant oligomers which avoid unwanted side effects of the natural unmodified oligomer by elimination of non-specific binding to cellular proteins and inappropriate cleavage of non-targeted RNA heteroduplexes.

Claims 14-16 and 23-25 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 1-13, 17-22 and 26-33 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen A Canella/

Primary Examiner, Art Unit 1643